=> file reg
FILE 'REGISTRY' ENTERED AT 17:14:38 ON 19 SEP 2002
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES: 18 SEP 2002 HIGHEST RN 452896-77-4
DICTIONARY FILE UPDATES: 18 SEP 2002 HIGHEST RN 452896-77-4

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP
PROPERTIES for more information. See STNote 27, Searching Properties
in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d rn cn l11

L11 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN 59865-13-3 REGISTRY
CN Cyclosporin A (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 1,4,7,10,13,16,19,22,25,28,31-Undecaazacyclotritriacontane, cyclic peptide deriv.
OTHER NAMES:
CN 7: PN: WO0002548 PAGE: 30 claimed protein
CN Antibiotic S 7481F1
CN Ciclosporin
CN Cipol N
CN Consupren
CN Cyclosporin
CN Cyclosporine
CN Cyclosporine A
CN Cyclo[L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl-(3R,4R,6E)-6,7-didehydro-3-hydroxy-N,4-dimethyl-L-2-aminooctanoyl-L-2-aminobutanoyl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl]
CN Neoplanta
CN Neoral
CN OL 27-400
CN Ramihyphin A
CN S-Neoral
CN Sandimmun
CN Sandimmun Neoral
CN Sandimmune
CN Sang-35
CN SDZ-OXL 400

=> d rn cn l12

L12 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN 85233-19-8 REGISTRY

CN Glycine, N,N'-[1,2-ethanediylbis(oxy-2,1-phenylene)]bis[N-(carboxymethyl)-
(9CI) (CA INDEX NAME)
OTHER NAMES:
CN 1,2-Bis(2-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid
CN 1,2-Bis(o-aminophenoxy)ethane-N,N,N',N'-tetraacetic acid
CN **BAPTA**

=> d rn cn l24

L24 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2002 ACS
RN 7440-70-2 REGISTRY
CN **Calcium (8CI, 9CI)** (CA INDEX NAME)
OTHER NAMES:
CN Atomic calcium
CN Blood-coagulation factor IV
CN Calcium atom
CN Calcium element
CN Praval

=> file caplus; d que l7; d que l17
FILE 'CAPLUS' ENTERED AT 16:50:37 ON 20 SEP 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1907 - 20 Sep 2002 VOL 137 ISS 13
FILE LAST UPDATED: 19 Sep 2002 (20020919/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

L1 (12990) SEA FILE=CAPLUS ABB=ON PLU=ON HEPATITIS B
L2 (5182) SEA FILE=CAPLUS ABB=ON PLU=ON HBV
L3 (13404) SEA FILE=CAPLUS ABB=ON PLU=ON L1 OR L2
L4 (594540) SEA FILE=CAPLUS ABB=ON PLU=ON CALCIUM
L5 (108) SEA FILE=CAPLUS ABB=ON PLU=ON L3 AND L4
L6 (40920) SEA FILE=CAPLUS ABB=ON PLU=ON CYTOSOLIC
L7 4 SEA FILE=CAPLUS ABB=ON PLU=ON L5 AND L6

```
L8  (     12990)SEA FILE=CAPLUS ABB=ON  PLU=ON  HEPATITIS B
L9  (      5182)SEA FILE=CAPLUS ABB=ON  PLU=ON  HBV
L10 (     13404)SEA FILE=CAPLUS ABB=ON  PLU=ON  L8 OR L9
L11 (    594540)SEA FILE=CAPLUS ABB=ON  PLU=ON  CALCIUM
L12 (         1)SEA FILE=REGISTRY ABB=ON  PLU=ON  "CYCLOSPORIN A"/CN
L13 (         1)SEA FILE=REGISTRY ABB=ON  PLU=ON  BAPTA/CN
L14 (     11534)SEA FILE=CAPLUS ABB=ON  PLU=ON  L12
L15 (     16739)SEA FILE=CAPLUS ABB=ON  PLU=ON  CYCLOSPORIN? OR SDZ OXL 400 OR
                OL 27 400 OR L14
L16 (      2201)SEA FILE=CAPLUS ABB=ON  PLU=ON  L13 OR BAPTA
L17           3 SEA FILE=CAPLUS ABB=ON  PLU=ON  L10 AND (L15 OR L16) AND L11


=> s l7 or l17
L73           6 L7 OR L17

=> file medline
FILE 'MEDLINE' ENTERED AT 16:50:50 ON 20 SEP 2002

 FILE LAST UPDATED: 19 SEP 2002 (20020919/UP).  FILE COVERS 1958 TO DATE.

 On June 9, 2002, MEDLINE was reloaded.  See HELP RLOAD for details.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2002 vocabulary.  Enter HELP THESAURUS for details.

 THIS FILE CONTAINS CAS REGISTRY NUMBERS FOR EASY AND ACCURATE
 SUBSTANCE IDENTIFICATION.

=> d que l28; d que l30
L18       26056 SEA FILE=MEDLINE ABB=ON  PLU=ON  HEPATITIS B+NT/CT
L19        9269 SEA FILE=MEDLINE ABB=ON  PLU=ON  HEPATITIS B VIRUS/CT OR
                HEPATITIS B VIRUS, WOODCHUCK/CT
L20       14561 SEA FILE=MEDLINE ABB=ON  PLU=ON  CYCLOSPORINE/CT
L22       16413 SEA FILE=MEDLINE ABB=ON  PLU=ON  CALCIUM CHANNELS+NT/CT
L23      167679 SEA FILE=MEDLINE ABB=ON  PLU=ON  CALCIUM/CT
L27       22202 SEA FILE=MEDLINE ABB=ON  PLU=ON  CALCIUM CHANNEL BLOCKERS/CT
L28           1 SEA FILE=MEDLINE ABB=ON  PLU=ON  L20 AND (L18 OR L19) AND (L22
                OR L23 OR L27)



L18       26056 SEA FILE=MEDLINE ABB=ON  PLU=ON  HEPATITIS B+NT/CT
L19        9269 SEA FILE=MEDLINE ABB=ON  PLU=ON  HEPATITIS B VIRUS/CT OR
                HEPATITIS B VIRUS, WOODCHUCK/CT
L24           6 SEA FILE=MEDLINE ABB=ON  PLU=ON  XIP PROTEIN/CN
L29           5 SEA FILE=MEDLINE ABB=ON  PLU=ON  (L18 OR L19) AND L24
L30           2 SEA FILE=MEDLINE ABB=ON  PLU=ON  L29 AND INHIBIT?/TI


=> s l28 or l30
L74           3 L28 OR L30

=> file embase; d que l40; d que l41; d que l42; d que l48
FILE 'EMBASE' ENTERED AT 16:51:29 ON 20 SEP 2002
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 FILE COVERS 1974 TO 19 Sep 2002 (20020919/ED)

 EMBASE has been reloaded. Enter HELP RLOAD for details.
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This file contains CAS Registry Numbers for easy and accurate substance identification.

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L31       15932 SEA FILE=EMBASE ABB=ON  PLU=ON  HEPATITIS B/CT
L32       13191 SEA FILE=EMBASE ABB=ON  PLU=ON  HEPATITIS B VIRUS/CT
L33       29350 SEA FILE=EMBASE ABB=ON  PLU=ON  CYCLOSPORIN A/CT
L34       15335 SEA FILE=EMBASE ABB=ON  PLU=ON  CALCIUM CHANNEL BLOCKING
                AGENT/CT
L35         192 SEA FILE=EMBASE ABB=ON  PLU=ON  CALCIUM CHANNEL AFFECTING
                AGENT/CT
L39       82538 SEA FILE=EMBASE ABB=ON  PLU=ON  CALCIUM/CT
L40           1 SEA FILE=EMBASE ABB=ON  PLU=ON  (L31 OR L32) AND L33 AND ((L34
                OR L35) OR L39)


L31       15932 SEA FILE=EMBASE ABB=ON  PLU=ON  HEPATITIS B/CT
L32       13191 SEA FILE=EMBASE ABB=ON  PLU=ON  HEPATITIS B VIRUS/CT
L36        1964 SEA FILE=EMBASE ABB=ON  PLU=ON  BAPETA OR BAPTA
L41           0 SEA FILE=EMBASE ABB=ON  PLU=ON  L36 AND (L31 OR L32)


L31       15932 SEA FILE=EMBASE ABB=ON  PLU=ON  HEPATITIS B/CT
L32       13191 SEA FILE=EMBASE ABB=ON  PLU=ON  HEPATITIS B VIRUS/CT
L33       29350 SEA FILE=EMBASE ABB=ON  PLU=ON  CYCLOSPORIN A/CT
L37         278 SEA FILE=EMBASE ABB=ON  PLU=ON  XIP OR HBX
L42           3 SEA FILE=EMBASE ABB=ON  PLU=ON  (L31 OR L32) AND L33 AND L37


L31       15932 SEA FILE=EMBASE ABB=ON  PLU=ON  HEPATITIS B/CT
L32       13191 SEA FILE=EMBASE ABB=ON  PLU=ON  HEPATITIS B VIRUS/CT
L33       29350 SEA FILE=EMBASE ABB=ON  PLU=ON  CYCLOSPORIN A/CT
L43       17504 SEA FILE=EMBASE ABB=ON  PLU=ON  L33/MAJ
L44       10672 SEA FILE=EMBASE ABB=ON  PLU=ON  L43 (L) (AE OR CR OR DT OR PD
                OR IV OR PO)/CT
L46        4742 SEA FILE=EMBASE ABB=ON  PLU=ON  (L31 OR L32) (L) DT/CT
L47          13 SEA FILE=EMBASE ABB=ON  PLU=ON  L46 AND L44
L48           2 SEA FILE=EMBASE ABB=ON  PLU=ON  L47 AND (ENCEPHALO? OR
                BIOPSY)/TI

=> s l40 or l42 or l48
L75           5 L40 OR L42 OR L48

=> file wpid; d que l58; d que l61; d que l62
FILE 'WPIDS' ENTERED AT 16:52:03 ON 20 SEP 2002
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FILE LAST UPDATED: 19 SEP 2002              <20020919/UP>
MOST RECENT DERWENT UPDATE            200260   <200260/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> The BATCH option for structure searches has been
    enabled in WPINDEX/WPIDS and WPIX  >>>

>>> PATENT IMAGES AVAILABLE FOR PRINT AND DISPLAY >>>

>>> FOR DETAILS OF THE PATENTS COVERED IN CURRENT UPDATES,
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SEE http://www.derwent.com/dwpi/updates/dwpicov/index.html <<<

>>> FOR A COPY OF THE DERWENT WORLD PATENTS INDEX STN USER GUIDE, PLEASE VISIT:
http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER GUIDES, PLEASE VISIT:
http://www.derwent.com/userguides/dwpi_guide.html <<<

```
L49         2680 SEA FILE=WPIDS ABB=ON  PLU=ON  HEPATITIS B
L52           28 SEA FILE=WPIDS ABB=ON  PLU=ON  BAPETA OR BAPTA
L54          598 SEA FILE=WPIDS ABB=ON  PLU=ON  HBV
L55         2806 SEA FILE=WPIDS ABB=ON  PLU=ON  HEP? (W) B
L58            0 SEA FILE=WPIDS ABB=ON  PLU=ON  (L49 OR L54 OR L55) AND L52


L49         2680 SEA FILE=WPIDS ABB=ON  PLU=ON  HEPATITIS B
L50         1285 SEA FILE=WPIDS ABB=ON  PLU=ON  CYCLOSPORIN?
L51        99329 SEA FILE=WPIDS ABB=ON  PLU=ON  CALCIUM
L54          598 SEA FILE=WPIDS ABB=ON  PLU=ON  HBV
L55         2806 SEA FILE=WPIDS ABB=ON  PLU=ON  HEP? (W) B
L57            3 SEA FILE=WPIDS ABB=ON  PLU=ON  (L49 OR L54 OR L55) AND L50 AND
                 L51
L61            1 SEA FILE=WPIDS ABB=ON  PLU=ON  L57 AND HEPATITIS/TI


L49         2680 SEA FILE=WPIDS ABB=ON  PLU=ON  HEPATITIS B
L51        99329 SEA FILE=WPIDS ABB=ON  PLU=ON  CALCIUM
L54          598 SEA FILE=WPIDS ABB=ON  PLU=ON  HBV
L55         2806 SEA FILE=WPIDS ABB=ON  PLU=ON  HEP? (W) B
L60            9 SEA FILE=WPIDS ABB=ON  PLU=ON  (L49 OR L54 OR L55) AND L54 AND
                 L51
L62            4 SEA FILE=WPIDS ABB=ON  PLU=ON  L60 AND HEPATITIS B/TI

=> s l61 or l62
L76            4 L61 OR L62

=> file biosis; d que l69; d que l71; d que l72
FILE 'BIOSIS' ENTERED AT 16:53:49 ON 20 SEP 2002
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FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 18 September 2002 (20020918/ED)


L63        36835 SEA FILE=BIOSIS ABB=ON  PLU=ON  HEPATITIS B
L64        37280 SEA FILE=BIOSIS ABB=ON  PLU=ON  CYCLOSPORIN?
L65       371482 SEA FILE=BIOSIS ABB=ON  PLU=ON  CALCIUM
L69            0 SEA FILE=BIOSIS ABB=ON  PLU=ON  L63 AND L64 AND L65
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L63       36835 SEA FILE=BIOSIS ABB=ON  PLU=ON  HEPATITIS B
L65      371482 SEA FILE=BIOSIS ABB=ON  PLU=ON  CALCIUM
L66         366 SEA FILE=BIOSIS ABB=ON  PLU=ON  XIP OR HBX
L71           1 SEA FILE=BIOSIS ABB=ON  PLU=ON  L63 AND L66 AND L65


L63       36835 SEA FILE=BIOSIS ABB=ON  PLU=ON  HEPATITIS B
L67        2434 SEA FILE=BIOSIS ABB=ON  PLU=ON  BAPTA OR BAPETA
L72          40 SEA FILE=BIOSIS ABB=ON  PLU=ON  L63 AND L67

=> dup rem l74 l73 l76 l75 l71
FILE 'MEDLINE' ENTERED AT 16:54:24 ON 20 SEP 2002

FILE 'CAPLUS' ENTERED AT 16:54:24 ON 20 SEP 2002
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PROCESSING COMPLETED FOR L74
PROCESSING COMPLETED FOR L73
PROCESSING COMPLETED FOR L76
PROCESSING COMPLETED FOR L75
PROCESSING COMPLETED FOR L71
L77           16 DUP REM L74 L73 L76 L75 L71 (3 DUPLICATES REMOVED)
                 ANSWERS '1-3' FROM FILE MEDLINE
                 ANSWERS '4-8' FROM FILE CAPLUS
                 ANSWERS '9-11' FROM FILE WPIDS
                 ANSWERS '12-16' FROM FILE EMBASE

=> d ibib ab l77 1-16

L77  ANSWER 1 OF 16     MEDLINE                          DUPLICATE 2
ACCESSION NUMBER:    2001695488     MEDLINE
DOCUMENT NUMBER:     21608565   PubMed ID: 11743208
TITLE:               Calcium signaling by HBx protein in hepatitis B virus DNA
                     replication.
COMMENT:             Comment in: Science. 2001 Dec 14;294(5550):2299-300
AUTHOR:              Bouchard M J; Wang L H; Schneider R J
CONTRACT NUMBER:     F32CA-4476 (NCI)
     ROICA-565633 (NCI)
SOURCE:              SCIENCE, (2001 Dec 14) 294 (5550) 2376-8.
                     Journal code: 0404511. ISSN: 0036-8075.
PUB. COUNTRY:        United States
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals
ENTRY MONTH:         200201
ENTRY DATE:          Entered STN: 20011217
                     Last Updated on STN: 20020125
                     Entered Medline: 20020114
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AB Hepatitis B virus (HBV) infects more than 300 million people and is a leading cause of liver cancer and disease. The HBV HBx protein is essential for infection; HBx activation of Src is important for HBV DNA replication. In our study, HBx activated cytosolic calcium-dependent proline-rich tyrosine kinase-2 (Pyk2), a Src kinase activator. HBx activation of HBV DNA replication was blocked by inhibiting Pyk2 or calcium signaling mediated by mitochondrial calcium channels, which suggests that HBx targets mitochondrial calcium regulation. Reagents that increased cytosolic calcium substituted for HBx protein in HBV DNA replication. Thus, alteration of cytosolic calcium was a fundamental requirement for HBV replication and was mediated by HBx protein.

L77 ANSWER 2 OF 16 MEDLINE
ACCESSION NUMBER: 1998344077 MEDLINE
DOCUMENT NUMBER: 98344077 PubMed ID: 9677410
TITLE: Liver-specific enhancer II is the target for the p53-mediated **inhibition** of hepatitis B viral gene expression.
AUTHOR: Lee H; Kim H T; Yun Y
CORPORATE SOURCE: Signal Transduction Laboratory, Mogam Biotechnology Research Institute, 341 Pojungri, Koosungmyon, Yongingoon, Kyunggido 449-910, Korea.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1998 Jul 31) 273 (31) 19786-91.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19980917
Last Updated on STN: 19980917
Entered Medline: 19980910

AB Here, we established the inhibitory mechanism of p53 on hepatitis B viral gene expression using HepG2 cells. Our results are as follows. First, p53 down-regulated the activities of all four promoters of hepatitis B virus (HBV), suggestive of the presence of a common element mediating the p53-dependent transcriptional repression. Second, employing the 5'-deletion constructs of the pregenomic/core promoter, the liver-specific enhancer II region was localized as a target for the p53-mediated transcriptional repression. Third, in a detailed analysis of the enhancer II region, the 5'-proximal 31-base pair region was defined as a p53-repressible element. Throughout the study, p53-mediated repression was rescued upon coexpression of the X-gene product, HBx. Finally, in an electrophoretic mobility shift assay, the defined p53-repressible element did not bind purified p53 directly, but shifted three bands in HepG2 nuclear extract, two of which was supershifted upon addition of p53 monoclonal antibody. These results display a novel mechanism of p53-dependent transcriptional repression in which p53 negatively regulates the viral-specific DNA enhancer through protein to protein interaction with an enhancer-binding protein. At the same time, the results indicate that p53 plays a defensive role against HBV by transcriptionally repressing the HBV core promoter through liver-specific enhancer II and HBx is required to counteract this inhibitory function of p53.

L77 ANSWER 3 OF 16 MEDLINE
ACCESSION NUMBER: 1998139062 MEDLINE
DOCUMENT NUMBER: 98139062 PubMed ID: 9499022
TITLE: Cloning and characterization of a novel hepatitis B virus x binding protein that **inhibits** viral replication.
AUTHOR: Melegari M; Scaglioni P P; Wands J R

CORPORATE SOURCE: Molecular Hepatology Laboratory, Massachusetts General Hospital Cancer Center, and Harvard Medical School, Charlestown 02129, USA.
CONTRACT NUMBER: CA-35711 (NCI)
SOURCE: JOURNAL OF VIROLOGY, (1998 Mar) 72 (3) 1737-43.
Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AF029890
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980319
Last Updated on STN: 19980319
Entered Medline: 19980312

AB The hepatitis B virus and the mammalian hepadnavirus genomes encode for a short open reading frame called x. Expression of the protein product (HBx) appears necessary for establishment of natural infection. However, in vitro studies have suggested a multifunctional role for HBx as an indirect transcriptional transactivator of a variety of different viral and cellular promoters. Indeed, HBx has no known direct DNA binding properties but may interact with transcription factors as well as activate intracellular signaling pathways associated with cell growth. To further address the possible functional role of HBx in the life cycle of hepatitis B virus, we performed an analysis using the yeast two-hybrid system to screen a cDNA library derived from a hepatocellular carcinoma cell line with a HBx fusion bait in an attempt to identify cellular partners that may bind to and alter the biologic properties of HBx. A HBx-interacting protein that specifically complexes with the carboxy terminus of wild-type HBx was identified and designated XIP. This 9.6-kDa protein is capable of binding to HBx in vitro, and transient and stable expression in hepatocellular carcinoma cells abolishes the transactivation properties of HBx on luciferase constructs driven by AP-1 and endogenous hepatitis B virus enhancer/promoter elements. Investigation of the role of XIP in hepatitis B virus replication in differentiated hepatocellular carcinoma cells revealed that XIP expression reduces wild-type hepatitis B virus replication to levels observed following transfection with an HBx-minus virus. In contrast, the replication levels of the duck hepatitis B virus, a hepadnavirus that lacks the x open reading frame, were unchanged in the context of XIP expression. We propose that one of the physiologic functions of the cellular protein XIP is to negatively regulate HBx activity and thus to alter the replication life cycle of the virus.

L77 ANSWER 4 OF 16 CAPLUS COPYRIGHT 2002 ACS DUPLICATE 1
ACCESSION NUMBER: 2002:294165 CAPLUS
DOCUMENT NUMBER: 136:304036
TITLE: Inhibition of the Src kinase family pathway as a method of treating **HBV** infection and hepatocellular carcinoma
INVENTOR(S): Schneider, Robert J.; Klein, Nicola
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 37 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002045191	A1	20020418	US 2001-955006	20010917

PRIORITY APPLN. INFO.: US 2000-232892P P 20000915
AB The present invention relates to therapeutic protocols and pharmaceutical compns. designed to target HBx mediated activation of Src kinase, members of the Src tyrosine kinase family and components of the Src kinase family signal transduction pathways for the treatment of **HBV** (**hepatitis B** virus) infection and related disorders and diseases, such as hepatocellular carcinoma (HCC). The invention further relates to pharmaceutical compns. for the treatment of **HBV** infection targeted to HBx and its essential activities required to sustain **HBV** replication. The invention is based, in part, on the Applicants' discovery that activation of Src kinase signaling cascades play a fundamental role in mammalian hepadnavirus replication. Applicants have demonstrated that HBx mediates activation of the Src family of kinases and that this activation is a crit. function provided by HBx for mammalian hepadnavirus replication.

L77 ANSWER 5 OF 16 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:158385 CAPLUS
DOCUMENT NUMBER: 136:205441
TITLE: Enantiomers of S-adenosyl-L-methionine
INVENTOR(S): Hebert, Rolland F.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 7 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002025926	A1	20020228	US 2001-943243	20010830

PRIORITY APPLN. INFO.: US 2000-229151P P 20000830
AB Enantiomers of S-adenosyl-l-methionine, their stable salts and their uses are described. These compns. possess potent activity in treating various conditions involving hypomethylation and transulfuration reactions and are valuable for use as active constituents in pharmaceutical compns. For example, (S,S)-S-adenosylmethionine was prepd. and stabilized using p-toluene sulfonate. (S,S)-S-adenosylmethionine enteric-coated tablets (400 mg) were administered twice daily for 14 days or until remission of depression symptoms in an open, non-blind study to 10 volunteers (one patient declined to continue the study after beginning). All patients had normal results on pre-study medical examns., including lab. examns. Eight of the nine patients who completed the trial improved over the 14 days, while one patient had no change at all. No side effects were noted or reported by any of the patients nor as measured by lab. or phys. examn. (S, S)-S-adenosylmethionine 400 mg twice daily appeared to be safe and effective in this small, non-blinded study of depression.

L77 ANSWER 6 OF 16 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:300514 CAPLUS
DOCUMENT NUMBER: 134:331617
TITLE: Oil-in-water emulsion compositions for polyfunctional active ingredients
INVENTOR(S): Chen, Feng-jing; Patel, Mahesh V.
PATENT ASSIGNEE(S): Lipocine, Inc., USA
SOURCE: PCT Int. Appl., 82 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001028555	A1	20010426	WO 2000-US28835	20001018
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002107265	A1	20020808	US 1999-420159	19991018

PRIORITY APPLN. INFO.: US 1999-420159 A 19991018

AB Pharmaceutical oil-in-water emulsions for delivery of polyfunctional active ingredients with improved loading capacity, enhanced stability, and reduced irritation and local toxicity are described. Emulsions include an aq. phase, an oil phase comprising a structured triglyceride, and an emulsifier. The structured triglyceride of the oil phase is substantially free of triglycerides having three medium chain (C6-C12) fatty acid moieties, or a combination of a long chain triglyceride and a polarity-enhancing polarity modifier. The present invention also provides methods of treating an animal with a polyfunctional active ingredient, using dosage forms of the pharmaceutical emulsions. For example, an emulsion was prepd., with **cyclosporin** A as the polyfunctional active ingredient dissolved in an oil phase including a structured triglyceride (Captex 810D) and a long chain triglyceride (safflower oil). The compn. contained (by wt.) **cyclosporin** A 1.0, Captex 810D 5.0, safflower oil 5.0, BHT 0.02, egg phospholipid 2.4, dimyristoylphosphatidyl glycerol 0.2, glycerol 2.25, EDTA 0.01, and water up to 100%, resp.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L77 ANSWER 7 OF 16 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:491156 CAPLUS

DOCUMENT NUMBER: 135:225821

TITLE: Inducible expression of the .alpha.2-macroglobulin signaling receptor in response to antigenic stimulation: a study of second messenger generation

AUTHOR(S): Bhattacharjee, Gourab; Misra, Uma K.; Gawdi, Govind; Cianciolo, George; Pizzo, Salvatore V.

CORPORATE SOURCE: Department of Pathology, Duke University Medical Center, Durham, NC, 27710, USA

SOURCE: Journal of Cellular Biochemistry (2001), 82(2), 260-270
CODEN: JCEBD5; ISSN: 0730-2312

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Thioglycollate (TG)-elicited murine, peritoneal macrophages express two receptors for activated forms of the proteinase inhibitor .alpha.2-macroglobulin (.alpha.2M*)-namely, the low d. lipoprotein receptor-related protein (LRP) and the .alpha.2M signaling receptor (.alpha.2MSR). The authors now report that resident peritoneal macrophages express only 400 .alpha.2MSR receptors/cell compared to 5000 receptor/TG-elicited macrophage. By contrast, LRP expression is only 2-2.5-fold greater on elicited cells. The low level of .alpha.2MSR expression by resident cells is insufficient to trigger signal

transduction in contrast to TG-elicited cells which when exposed to .alpha.2M* demonstrate a rapid rise in inositol 1,4,5-trisphosphate and a concomitant increase in **cytosolic** free Ca2+. The authors then studied a variety of prepns. injected s.c. for their ability to upregulate .alpha.2MSR. Macroaggregated bovine serum albumin (macroBSA) injection upregulated .alpha.2MSR and triggered signaling responses by splenic macrophages. Non-aggregated BSA injection alone or in the presence of alum, by contrast, did not alter .alpha.2MSR expression. Recombivax (**hepatitis B** antigen adsorbed to alum) injection also upregulated .alpha.2MSR on splenic macrophages while the alum carrier had no effect. The authors conclude that macrophage .alpha.2M* receptors are inducible and their expression may be regulated, in part, by potential antigens.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L77 ANSWER 8 OF 16 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:467434 CAPLUS
DOCUMENT NUMBER: 133:277687
TITLE: Crystal Structure of the Carbohydrate Recognition Domain of the H1 Subunit of the Asialoglycoprotein Receptor
AUTHOR(S): Meier, Markus; Bider, Marc D.; Malashkevich, Vladimir N.; Spiess, Martin; Burkhard, Peter
CORPORATE SOURCE: M.E. Muller Institute for Structural Biology, Univ. Basel, Basel, Switz.
SOURCE: Journal of Molecular Biology (2000), 300(4), 857-865
CODEN: JMOBAK; ISSN: 0022-2836
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The human asialoglycoprotein receptor (ASGPR), also called hepatic lectin, is an integral membrane protein and is responsible for the clearance of de-sialylated, galactose-terminal glycoproteins from the circulation by receptor-mediated endocytosis. It can be subdivided into four functional domains: the **cytosolic** domain, the transmembrane domain, the stalk and the carbohydrate recognition domain (CRD). The galactose-binding domains belong to the superfamily of C-type (**calcium**-dependent) lectins, in particular to the long-form subfamily with three conserved intramol. disulfide bonds. It is able to bind terminal non-reducing galactose residues and N-acetyl-galactosamine residues of de-sialylated tri or tetra-antennary N-linked glycans. The ASGPR is a potential liver-specific receptor for **hepatitis B** virus and Marburg virus and has been used to target exogenous mols. specifically to hepatocytes for diagnostic and therapeutic purposes. Here, we present the X-ray crystal structure of the carbohydrate recognition domain of the major subunit H1 at 2.3 .ANG. resoln. While the overall fold of this and other known C-type lectin structures are well conserved, the positions of the bound **calcium** ions are not, indicating that the fold is stabilized by alternative mechanisms in different branches of the C-type lectin family. It is the first CRD structure where three **calcium** ions form an integral part of the structure. In addn., the structure provides direct confirmation for the conversion of the ligand-binding site of the mannose-binding protein to an asialoglycoprotein receptor-like specificity suggested by Drickamer and colleagues. In agreement with the prediction that the coiled-coil domain of the ASGPR is sepd. from the CRD and its N-terminal disulfide bridge by several residues, these residues are indeed not .alpha.-helical, while in tetranectin they form an .alpha.-helical coiled-coil. (c) 2000 Academic Press.

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L77 ANSWER 9 OF 16 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 2001-625781 [72] WPIDS
DOC. NO. CPI: C2001-186395
TITLE: New compositions containing entecavir at low doses, useful for treating **hepatitis B** virus infection by once daily administration.
DERWENT CLASS: A96 B02
INVENTOR(S): COLONNO, R J; DESAI, D; FAKES, M G; HARIANAWALA, A; SPROCKEL, O L
PATENT ASSIGNEE(S): (COLO-I) COLONNO R J; (DESA-I) DESAI D; (FAKE-I) FAKES M G; (HARI-I) HARIANAWALA A; (SPRO-I) SPROCKEL O L; (BRIM) BRISTOL-MYERS SQUIBB CO
COUNTRY COUNT: 93
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001064221	A1	20010907	(200172)*	EN	27
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
US 2001033864	A1	20011025	(200172)		
CN 1310999	A	20010905	(200201)		
AU 2001029775	A	20010912	(200204)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2001064221	A1		WO 2001-US2630	20010126
US 2001033864	A1	Provisional	US 2000-185672P	20000229
		Provisional	US 2000-221313P	20000728
			US 2001-792576	20010223
CN 1310999	A		CN 2000-126403	20000829
AU 2001029775	A		AU 2001-29775	20010126

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001029775	A	Based on	WO 200164221

PRIORITY APPLN. INFO: US 2000-221313P 20000728; US 2000-185672P 20000229; US 2001-792576 20010223

AB WO 200164221 A UPAB: 20011206
NOVELTY - A novel pharmaceutical composition for once a day administration to treat **hepatitis B** virus (**HBV**) infection comprises a carrier and 0.001-25 mg of entecavir.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a pharmaceutical composition for oral administration of a low dose of entecavir comprising 0.001-10 mg of entecavir adhered to a carrier substrate;

(2) a pharmaceutical composition for oral administration of a low dose of entecavir comprising entecavir coated using an adhesive substance to a carrier, a lubricant, and a disintegrant, where:

(a) the entecavir is present at 0.001-10 wt.% of the composition;

(b) the adhesive substance is present at 0.01-10 wt.% of the composition;

(c) the carrier substrate is present at 80-95 wt.% of the composition;

(d) the disintegrant is present at 1-7 wt.% of the composition; and

(e) the lubricant is present at 0.1-5 wt.% of the composition;

(3) a low dose entecavir tablet composition comprising:

(a) 0.01% entecavir, 93.24% microcrystalline cellulose, 4.0% crospovidone, 2.50% povidone, and 0.25% magnesium stearate; or

(b) 1.0% entecavir, 90.0% mannitol, 4.0% crosscarmellose sodium, 2.50% methyl cellulose and 2.50% stearic acid; or

(c) 0.5% entecavir, 90.00% lactose monohydrate, 32.50% microcrystalline cellulose, 4.0% crospovidone, 2.50% povidone, and 0.50% magnesium stearate; or 0.1% entecavir, 60.00% lactose monohydrate, 35.59% microcrystalline cellulose, 4.0% crospovidone, 0.01% povidone, and 0.5% magnesium stearate; the percentages being on a weight/weight basis;

(4) a low dose entecavir capsule composition comprising:

(a) 10.0% entecavir, 82.03% microcrystalline cellulose, 4.00% crospovidone, 2.50% povidone, 0.25% magnesium stearate, and 1.22% HCL; or

(b) 0.05% entecavir, 93.20% dicalcium phosphate, 4.00% crospovidone, 2.50% hydroxypropyl cellulose; and 0.25% magnesium stearate; the percentages being on a weight/weight basis;

(5) a method of preparing a pharmaceutical composition for oral administration containing a low dose of a soluble active agent comprising:

(a) dissolving the active agent and an adhesive substance in a solvent;

(b) spraying the solution from (a) onto a carrier substrate while the carrier substrate is in motion;

(c) drying the coated carrier substrate from (b) to remove the solvent; and

(d) combining the dried coated carrier substrate from (c) with other desired ingredients to form the pharmaceutical composition.

ACTIVITY - Antiviral; Hepatotropic; Antiinflammatory.

MECHANISM OF ACTION - None given.

USE - The compositions containing entecavir are useful for treating **hepatitis B** virus (**HBV**) infection (claimed, see US5206244). The compositions can also be used for treating **HBV** patients co-infected with other viral or non-viral diseases, e.g. hepatitis C or HIV. The safety and antiviral activity of entecavir given for 28 days to human subjects with chronic **HBV** infection was studied in a randomized, double-blind, placebo-controlled, dose-escalating trial. Entecavir showed potent antiviral activity at all doses tested. The mean log reduction in **HBV** DNA viral levels in the blood at day 28 were 2.21, 2.25, 2.81, and 2.42 for the 0.05, 0.1, 0.5 and 1.0 mg once daily doses of entecavir respectively. Entecavir was well tolerated.

ADVANTAGE - The low dose entecavir compositions can be administered on a daily basis for effective control of **HBV** infection without undesirable side effects that can result from administration of the high dose regimen described in US5206244. The process of depositing the active substance on the carrier substrate can be controlled to minimize the agglomeration of the active substance/carrier substrate particles. This also prevents the separation of the entecavir from the substrate and minimizes the loss of entecavir during subsequent processing.

Dwg.0/0

L77 ANSWER 10 OF 16 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 1995-282427 [37] WPIDS
DOC. NO. CPI: C1995-127514
TITLE: **Hepatitis B** virus surface antigen granule contg. hepatitis delta virus antigen - prepared by co-transfecting liver cancer clone with plasmids

expressing large and small D antigens and HBsAg.
DERWENT CLASS: B04 D16
INVENTOR(S): CHEN, D; CHEN, P
PATENT ASSIGNEE(S): (NASC-N) NAT SCI COMMITTEE
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
TW 251319	A	19950711	(199537)*		23

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
TW 251319	A	TW 1992-108310	19921019

PRIORITY APPLN. INFO: TW 1992-108310 19921019
AB TW 251319 A UPAB: 19950921
A **Hepatitis B** virus (**HBV**) surface antigen granule carrying Hepatitis Delta virus (HDV) antigen is prepared using plasmid pS1X expressing **HBV** surface antigen and plasmids pSVLDAg-L and pSVLAg-S, expressing HDV large or small antigen, respectively as follows: (1) transfecting the plasmids into liver cancer clone by **calcium** phosphate precipitation and (2) purifying the virus granules, in which the **HBV** surface antigen granule carrying HDV is divided into two types: (i) it only contains the large D antigen and plasmid pSVLDAg-L and plasmid pS1X are cotransfected into the liver cancer clone; or (ii) it contains both the large D and small D antigens at the same time, and plasmids pSVLDAg-L, pSVLAg-S and pS1X are cotransfected into the liver cancer clone to jointly form a **HBV** /HDV composite granule; the small D antigen cannot be enveloped in the virus granule alone and enters the **HBV** antigen granule together with large D antigen. (GS1).
Dwg.0/7

L77 ANSWER 11 OF 16 WPIDS (C) 2002 THOMSON DERWENT
ACCESSION NUMBER: 1988-057770 [09] WPIDS
DOC. NO. NON-CPI: N1988-043915
DOC. NO. CPI: C1988-025707
TITLE: **Hepatitis B** surface antigen peptide - produced by cell line contg. S gene isolated from human hepatoma Alexander cells.
DERWENT CLASS: B04 D16 S03
INVENTOR(S): SHAUL, Y
PATENT ASSIGNEE(S): (YEDA) YEDA RES & DEV CO LTD
COUNTRY COUNT: 15
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 257507	A	19880302	(198809)*	EN	10
R: AT BE CH DE ES FR GB GR IT LI LU NL SE					
AU 8777133	A	19880218	(198815)		
JP 63132845	A	19880604	(198828)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE

EP 257507 A EP 1987-111890 19870817
JP 63132845 A JP 1987-203970 19870817

PRIORITY APPLN. INFO: IL 1986-79740 19860817
AB EP 257507 A UPAB: 19930923
Hepatitis B surface antigen (HBsAg) peptide produced by clone A126, the amino acid sequence of which corresponds to that of natural HBsAg is claimed. Also claimed is a cell line for the prodn. of HBsAg contg. the 5 gene complex which comprises the S gene TATA promoter, the SV40 like promoter and the pre-Si, pre-S2 and S gene coding regions.

The cell line uses an S gene isolated from Alexander cells, human hepatoma cells which constitutively overexpresses the HBsAg. The integrated **HBV** DNA in Alexander cells was isolated by molecular cloning and was characterised by restriction enzyme mapping and partial DNA sequence analysis. Each of 7 clones was inserted into CHO dhfr- cell line using the dhfr gene as a selective marker using the **calcium** phosphate coprecipitate technique. Only one clone, A126 produced significant amts. of HBsAg.

USE/ADVANTAGE - Large quantities of HBsAg can be produced which can be used as active ingredient in vaccines against **Hepatitis B** virus (**HBv**).

L77 ANSWER 12 OF 16 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002215754 EMBASE
TITLE: Color ultrasound-guided fine-needle cutting **biopsy** for the characterization of diffuse liver damage in critical bone marrow transplanted patients.
AUTHOR: Picardi M.; Muretto P.; De Rosa G.; Selleri C.; De Renzo A.; Persico M.; Rotoli B.
CORPORATE SOURCE: Prof. B. Rotoli, Divisione di Ematologia, Nuovo Policlinico, via S. Pansini 5, 80131 Naples, Italy. rotoli@unina.it
SOURCE: Haematologica, (2002) 87/6 (652-657).
Refs: 27
ISSN: 0390-6078 CODEN: HAEMAX
COUNTRY: Italy
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 014 Radiology
016 Cancer
025 Hematology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Background and Objectives. The optimal method for liver biopsy in patients with simultaneous bone marrow and liver impairment has not yet been established. New approaches (e.g. imaging-guided methods) for this procedure are needed. In spite of coagulopathy, immuno-suppression, anemia or ascites, we histologically characterized liver damage in a series of bone marrow transplanted patients using color-Doppler ultrasonography, which permits very keen visualization (and assessment) of hepatic parenchyma and vessels, and a fine needle for percutaneous biopsy. Design and Methods. We performed percutaneous liver biopsy using a Menghini-type automatic very fine cutting needle (1.2 mm, 18G) under color ultrasound guidance in 16 bone marrow transplanted adult patients consecutively seen in our units from 1998 to 2001. The patients had clinically defined diffuse serious liver damage; liver biopsy was performed between 3 and 10 months after allogeneic (n= 11) or autologous (n= 5) transplantation. Results. Fifteen patients tolerated the procedure well and had no

discomfort, while one patient developed intrahepatic hemorrhage. All liver biopsies were suitable for histologic examination and informative, revealing the specific etiology of liver damage: graft-versus-host disease in six patients, drug toxicity in five, hepatitis C virus acute reactivation in two, and in one each vanishing bile duct syndrome, nodular regenerative hyperplasia and hemo-chromatosis. Biopsy detected potentially injurious concomitant factors, e.g., occult intrahepatic hepatitis B virus infection and reactivation. Histology radically changed the presumptive clinical diagnosis in 10 of the 16 patients and led to successful treatment changes in six. Interpretation and Conclusions. Percutaneous biopsy with a small cutting needle under color ultrasound guidance carries a low risk of complications and provides reliable information regarding liver histology in critically ill patients, in the early stage after bone marrow transplantation. We suggest including this imaging-guided mini-invasive procedure to the standard work-up of post-transplant liver damage. .COPYRGT.2002, Ferrata Storti Foundation.

L77 ANSWER 13 OF 16 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001381715 EMBASE
TITLE: Cyclosporin A-induced **encephalopathy** after allogeneic bone marrow transplantation with prevention of graft-versus-host disease by tacrolimus.
AUTHOR: Takahata M.; Hashino S.; Izumiyama K.; Chiba K.; Suzuki S.; Asaka M.
CORPORATE SOURCE: Dr. M. Takahata, Third Dept. of Internal Medicine, Hokkaido Univ. School of Medicine, Kita-15, Nishi-7, Kita-ku, Sapporo 060-8638, Japan
SOURCE: Bone Marrow Transplantation, (2001) 28/7 (713-715).
Refs: 8
ISSN: 0268-3369 CODEN: BMTRE
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
025 Hematology
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB A 21-year-old woman with severe aplastic anemia received an allogeneic bone marrow transplant (allo-BMT) from an HLA-matched and ABO-matched sibling donor after conditioning with cyclophosphamide, rabbit ATG (Lymphoglobuline; Aventis-Pharma), and total lymphoid irradiation. She had a long history of cyclosporin A (CsA) therapy before conditioning. She complained of severe headache and convulsions on day 0, and findings on magnetic resonance images suggested CsA-induced encephalopathy. CsA was immediately stopped, and tacrolimus for prevention of graft-versus-host disease (GVHD) was started on day 2. Hematological engraftment was observed on day 14 without serious GVHD. Prompt diagnosis, replacement of immunosuppressive agents, and careful monitoring of serum drug concentrations are thought to have contributed to the patient's good clinical course, since CsA-induced encephalopathy tends to be recurrent but to improve completely without any sequelae.

L77 ANSWER 14 OF 16 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2001323828 EMBASE
TITLE: Nuclear factor of activated T cells (NFAT1-C) represses the enhancer II and pregenomic promoter (EnII/Cp) of hepatitis B virus (HBV) through its responsive site GGAGA and nullifies the **HBx**-driven transcriptional

activation.
AUTHOR: Joong Hyuk Lee; Hyune Mo Rho
CORPORATE SOURCE: H.M. Rho, School of Biological Sciences, Seoul National University, Seoul 151-742, Korea, Republic of. hyunerho@plaza.snu.ac.kr
SOURCE: IUBMB Life, (2001) 51/4 (255-261).
Refs: 40
ISSN: 1521-6543 CODEN: IULIF8
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The immunosuppressant cyclosporin A (CsA)-sensitive nuclear factor of activated T cells 1 (NFAT1) has been known to be a transcriptional regulator of cytokine and viral genes during the immune response. By analyses of serial deletion, mutation, and heterologous promoter assay, we report here that the CsA-sensitive NFAT1-C represses the transcriptional activity of enhancer II and pregenomic promoter (EnII/Cp) of HBV through the NFAT1-C responsive site (GGAGA, nt 1603-1618) and nullifies the **HBx**-driven transcriptional activation of the EnII/Cp of HBV in a dose-dependent manner. These results suggest that a CsA-sensitive NFAT1-C may control the viral activity in HBV-infected cells by inhibiting the EnII/Cp and nullifying the **HBx**-driven transcriptional activation.

L77 ANSWER 15 OF 16 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1999189729 EMBASE
TITLE: The proapoptotic effect of hepatitis B virus **HBx** protein correlates with its transactivation activity in stably transfected cell lines.
AUTHOR: Bergametti F.; Prigent S.; Luber B.; Benoit A.; Tiollais P.; Sarasin A.; Transy C.
CORPORATE SOURCE: C. Transy, Unite Recomb. Expression Genetique, (INSERM U163), Institut Pasteur, Paris, France
SOURCE: Oncogene, (6 May 1999) 18/18 (2860-2871).
Refs: 51
ISSN: 0950-9232 CODEN: ONCNES
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
016 Cancer
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The role of hepatitis B virus **HBx** protein in carcinogenesis associated with chronic viral infection remains ill-defined. Indeed, pleiotropic effects have been ascribed to **HBx**: in addition to its well-documented ability to indirectly stimulate transcription, the protein has been reported to affect cell growth, signal transduction, DNA repair and apoptosis. In this work, we generated Chang (CCL-13)-derived cell lines constitutively espressing wild type or mutant **HBx**, as a model of **HBx**-host cell interaction closer to the chronic infection setting, than the classically used transient expression systems. We document the potentiation by **HBx** of the apoptotic cell death pathway in the recipient cells. This effect is unlikely to rely on p53 activity since the protein is functionally inactivated in CCL-13. In addition, antioxidants and cyclosporin A failed to reduce the apoptotic response back to the normal level, suggesting that production of reactive oxygen species and calcineurin activation are not directly involved in the

proapoptotic effect of **HBx**. In contrast, our data show that transactivation and stimulation of apoptosis are tightly linked **HBx** activities. Finally, expression of transactivation-active protein did not result in detectable change in the pattern of MAP kinases phosphorylation nor did it affect the ability of the host cell to repair in vitro irradiated plasmid DNA.

L77 ANSWER 16 OF 16 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998410441 EMBASE
TITLE: The hepatitis B virus X protein activates nuclear factor of activated T cells (NF-AT) by a cyclosporin A-sensitive pathway.
AUTHOR: Lara-Pezzi E.; Armesilla A.L.; Majano P.L.; Redondo J.M.; Lopez-Cabrera M.
CORPORATE SOURCE: M. Lopez-Cabrera, Unidades de Biologia Molecular, Hospital de la Princesa, Universidad Autonoma de Madrid, 28006 Madrid, Spain. mlcabrera/princesa@hup.es
SOURCE: EMBO Journal, (1 Dec 1998) 17/23 (7066-7077).
Refs: 68
ISSN: 0261-4189 CODEN: EMJODG
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The X gene product of the human hepatitis B virus (**HBx**) is a transcriptional activator of various viral and cellular genes. We recently have determined that the production of tumor necrosis factor-.alpha. (TNF-.alpha.) by HBV-infected hepatocytes is transcriptionally upregulated by **HBx**, involving nuclear factor of activated T cells (NF-AT)-dependent activation of the TNF-.alpha. gene promoter. Here we show that **HBx** activates NF-AT by a cyclosporin A-sensitive mechanism involving dephosphorylation and nuclear translocation of the transcription factor. Luciferase gene expression assays demonstrated that **HBx** transactivates transcription through NF-AT-binding sites and activates a Gal4-NF-AT chimeric protein. DNA-protein interaction assays revealed that **HBx** induces the formation of NF-AT-containing DNA-binding complexes. Immunofluorescence analysis demonstrated that **HBx** induces the nuclear translocation of NF-AT, which can be blocked by the immunosuppressive drug cyclosporin A. Furthermore, immunoblot analysis showed that the **HBx**-induced activation and translocation of NF-AT are associated with its dephosphorylation. Thus, **HBx** may play a relevant role in the intrahepatic inflammatory processes by inducing locally the expression of cytokines that are regulated by NF-AT.

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